REMARKS AND ARGUMENTS

I. AMENDMENTS TO THE SPECIFICATION

Removal of hyperlink

Applicants have herein amended the specification to comply with the examiner's request to remove embedded hyperlinks (MPEP § 608.01), although Applicants submit that the hyperlink is only there to direct practitioners of the patent to a useful computer program.

II. CLAIM AMENDMENTS

The Applicants assert that these amendments add no new matter and their incorporation is respectfully requested.

Claims 1,-6, 9, 14 and 15 have been amended to better point out and describe the invention.

Claim 10 has been canceled. Support for the claim amendments are at least as follows;

Claim 1 at least at Figure 102.

Claim 2 at least at Figure 102.

Claim 3 at least at Figure 102.

Claim 4 at least at Figure 102.

Claim 5 at least at Figure 102.

Claim 6 at least at Figure 102.

Claim 9 at least at Figure 102.

Claim 14 at least at Figure 102.

Claim 15 at least at page 22, lines 13-16.

III REJECTIONS

A. The Rejection under 35 U.S.C. § 101

Claims 1-20 stand rejected under 35 U.S.C. § 101 as allegedly not being supported by either a specific and substantial asserted or a well-established utility. The general basis of the Examiner's rejection is that the data presented in Example 18 of the present specification is insufficient to establish a patentable utility for the presently claimed subject matter. Applicants respectfully traverse the rejection.

The Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility".

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed. However, when the condition to be diagnosed is specifically identified, the asserted utility is "specific".

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in Brenner v. Manson, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. § 2107.01, emphasis added). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility".

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. § 2107 II (B)(1)(ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the

facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The PTO also sets forth the evidentiary standard as to utility rejections. In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." In re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). See, also In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); In re Irons, 340 F.2d 974, 144 USPQ 351 (1965); In re Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout ex parte examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

The Data At Issue

The data at issue in the present Office Action is that which is presented in Example 18 of the current specification. Example 18 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR) based assay which allows one to quantitatively measure the level of gene expression for any gene in any sample of mRNA or cDNA produced from that mRNA. Moreover, as described in Example 18, a β-actin control is employed to ensure that the total amount of nucleic acid in all samples being tested is the same. Since use of the β-actin control assures that all tested samples contain the same amount of total nucleic acid and since the assay allows one to quantitatively measure the amount of expression for any specific gene of interest, the assay allows one to make clear, concise and reproducible

quantitative comparisons of "gene-specific" expression between two of more samples. In other words, the assay allows one to detect quantitative differences in gene expression between two or more different samples. Therefore, using this assay, one can determine whether any gene of interest is expressed at a higher or lower rate in a sample derived from a first tissue of interest (say, for example, a cancerous tumor tissue) than in a second tissue of interest (say, for example, a normal tissue).

It is exactly this type of comparison that is presented in Example 18 for the polypeptide-encoding nucleotide sequence referred to in the present specification as DNA68862-2546. More specifically, the data in Example 18 demonstrate that there is a detectable difference in DNA68862-2546 expression in at least one type of human melanoma tumor when compared to its normal human skin counterpart (detectably higher expression in the melanoma tumor than in the corresponding normal tissue);

Based upon these data, Applicants have asserted in the present patent application that this reproducible, quantitative difference in the level of expression of DNA68862-2546 can be exploited for diagnosing the presence of a particular type of melanoma tumor in a human subject. Applicants respectfully submit, however, that upon application of the appropriate legal standards described above, the proper conclusion is that the present application does disclose a patentable utility for the claimed invention.

In support of the outstanding rejection, the Examiner first relies on the Haynes et al., article (Haynes P.A. et al., Electrophoresis 19:1862-1871 (1998)). The Haynes paper is cited as proof that increased transcript levels do not necessarily equate with increased protein production. Applicants submit that the data and statements made by Haynes are not compelling. On page 1863, section 2.1, Hayes states that "Thus far, we have found a general trend but no strong correlation between protein and transcript levels." This means that Haynes has found that generally increased expression leads to increased protein levels, but does not assign a value either to this general trend nor to the correlation. In his concluding remarks on page 1870, Haynes admits that there a problems in his analysis due to technical difficulties "While it is currently possible to identify essentially any protein spots that can be visualized by common staining methods, it is apparent that without prior enrichment only a relatively small and highly

selected population of long-lived, highly expressed proteins is observed. There are many more proteins in a given cell which are not visualized by such methods. Frequently it is the low abundance proteins that execute key regulatory functions." This shows that Haynes et al., is only analyzing a small subpopulation of proteins, on which he bases his conclusion. If the gene has a level of transcription that equals translational levels of protein, but the protein is quickly degraded, then Haynes will not see it. Conversely, if the gene has a moderate level of transcription that equals moderate translational levels, but the protein has a long-half life, then Haynes will see it, and it will skew his results as the protein will appear highly expressed due to its long half life. If the gene has a level of transcription that equals translational levels of protein, but this is low abundance, then Haynes will not see it. While the Haynes paper is scientifically interesting, Applicants submit that it cannot be prior art as DNA68862-2546 is not analyzed, mentioned or taught by Haynes. Indeed, Haynes analyzed a yeast genome, not cancerous mammalian tissue, as was done with DNA68862-2546. The Applicants respectfully direct the Examiner's attention to papers by Kawamoto et al., (Gene 174:151-158 (1996)) and Yousef et al., (Cancer Res. 63:2223-2227 (2003)) submitted herewith that analyze human tissues including cancer.

Kawamoto et al., did broad expression profiling in mouse and human liver. Kawamoto et al, analyzed 959 human liver "gene signatures" which represent short pieces of genes. These gene signatures when analyzed, were narrowed down to 392 genes, of 81 were repeated frequently, and 311 which appeared only once. On page 153 and Table 1, Kawamoto shows a positive correlation between the abundance of the transcript and the protein concentration in the serum.

Yousef et al., was more specific and looked at the expression of Kallikrein genes in ovarian cancer. Yousef found that 7 Kallikrein genes were upregulated in ovarian cancer, and for 6 of the Kallikrein genes found a significant correlation between gene expression and protein concentration levels. So Yousef et al., analyzed both what Kallikrein genes were found in ovarian cancer, and of those genes, which were overexpressed and the protein level correlated with the amount of expression. See tables 1-3.

The Examiner also cites an editorial article by Hancock (J. Proteome Res. 3(4):685 (2004)). Hancock states that "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling." Applicants argue that Hancock is not prior art. Hancock cites provides no data, he simply states a conclusion. Hancock is an editorial article that is calling for a consortium on cancer markers with consistent nomenclature and validated markers, much like the Human Genome project is trying to do with the "GO gene" project. Hancock is not writing to present data and argue a scientific result, but to make a persuasive argument for funding; "I think that many people in the proteomics community would agree that federal granting agencies should be enticed to continue investments in basic proteomics technology. In addition, funding should be made available for basic science studies that will continue to generate biomarkers..." Applicants submit that while Hancock is impassioned, it has no bearing on DNA68862-2546, and should not be considered prior art.

In furtherance of the rejection the Examiner also relies on Hu et al., J. Proteome Res. 2:405-412(2003). The Examiner relies on the Hu et al., paper to state that genes with a 10 fold or greater change in expression level, there is a correlation with the expression level and a published role in the disease. Hu et al., uses breast cancer as the basis for this conclusion. Applicants submit that the Hu et al., paper does not provide support for the establishment of a baseline of expression data as being correlative with a tumour type. Applicants direct the Examiner's attention to Table 3 on page 412 of the Hu paper. In Table 3, expression of genes are compared in two different types of breast cancer, estrogen receptor positive (ER+)and estrogen receptor negative (ER-). For example, the gene KRTHB1 has an enormous 610.8 fold overexpression in ER- breast cancer but only a 1.0 fold overexpression in ER+ breast cancer. Applicants argue that for this and other genes in Table 3, it makes it more difficult to conclude if that particular gene plays a role in breast cancer. One of skill in the art upon discovering a 610.8 fold overexpression of a gene in breast cancer would certainly call that a "gene involved in breast cancer" but this broad assumption would only be correct for a certain subset of breast cancer tumors, those that are ER-. Hu et al., admits "that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." Applicants would make the same argument about the melanoma findings presented here. Applicants do not argue

that DNA68862-2546 is overexpressed in all melanoma, but like in the Hu et al., paper it was significantly overexpressed in the melanomas tested. Applicants submit that as long as DNA68862-2546 is overexpressed in a type of melanoma, then this is enough to meet the utility requirement.

In furtherance of the rejection, the Examiner cites Wang et al., TiPS 17: 276-279 (1996). The Wang et al., paper deals with mRNA based techniques, specifically differential display techniques, to validate potential therapeutic targets. The Examiner has cited the Wang paper as Wang indicates that differential display is but the first of many steps required in the discovery of a novel pharmacological target. Applicants find just the opposite of the Examiner. Applicants submit that the Wang et al., paper is actually a favourable reflection on the instant data stating on the Wang paper, page 279, right column;

"The application of mRNA differential display, and other techniques, for the isolation of novel genes associated with disease processes will no doubt facilitate the discovery of novel therapeutic targets and/or will help to understand the molecular mechanisms of disease."
This supports the Applicants approach that using PCR or microarray based system is a valid means of facilitating in the discovery of novel therapeutic targets involved in melanoma. Wang et al., is further cited by the Examiner "Therefore, further action should be taken to characterize the functions of a particular gene of interest, including isolation of full length cDNA, expression of the gene product for functional study and target validation for the importance of this gene in disease processes." Applicants submit that they have done as Wang suggests. Applicants have;
1. isolated and characterized the full length DNA68862-2546;
2. included in the specification Examples 6, 7, 8, and 9 which describe how to express DNA68862-2546 in E.coli, mammalian cells, yeast and baculovirus respectively;
3. found that DNA68862-2546 is overexpressed in disease tissue, specifically melanoma.
Applicants submit that Wang et al., does not specifically disclose or teach that DNA68862-2546 is overexpressed in melanoma, but if Wang does apply, then applicants have met all the factors that Wang suggests.

The two important aspects about the DNA68862-2546-related data presented in Example 18 are (1) there is a detectable difference in DNA68862-2546 gene expression between the

various tumor samples tested and their normal respective counterparts, and (2) the level of expression of DNA68862-2546 is detectably higher in the melanoma tumors tested and detectably lower in the corresponding normal skin tissues. The Examiner seems to focus on "how much higher" or "how much lower" (i.e., requiring Applicants to provide exact numbers), but Applicants submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful. What is important for the diagnostic utility asserted in the present application is (1) to be able to quantitatively compare the level of DNA68862-2546 expression in a tumor sample to a normal sample and (2) to detect a relative difference in the level of gene expression between the tumor and normal samples. The exact magnitude or size of that difference is irrelevant to the utility.

For example, the asserted utility relies only upon being able to detect a relative difference in the level of DNA68862-2546 expression in the tumor sample as compared to the normal sample, the exact magnitude thereof is not relevant. Thus, if one employs the described assay to quantitatively compare the level of DNA68862-2546 expression in, for example, (i) an human melanoma and (ii) a corresponding normal human skin sample, one of two results will be obtained. First, the investigator may find that the level of DNA68862-2546 expression in the unknown sample as compared to the known normal sample is either the same or detectably lower. In this case, no useful diagnostic information is obtained. However, if the investigator finds that the level of DNA68862-2546 expression is detectably higher in the sample of unknown pathology as compared to known normal sample, then useful diagnostic information is obtained. Therefore, knowledge of the fact that DNA68862-2546 is "more highly expressed" in one tissue as compared to another does "enable the skilled artisan to differentiate amongst expression levels" and, as such, does provide useful diagnostic information.

The Examiner cites as a final argument the work of Henikoff et al., Science 278: 609-614 (1997). The Henikoff paper deals with classification of gene paralogues and orthologues and how nature uses common motifs and gene divergence to create proteins with new function. Henikoff goes on to say that homology can be a boon understanding the gene's biological role. Applicant's have taken note of the Examiner's argument in light of Henikoff and reference the priority document 60/170,262 where Applicants disclose that the PRO3579 encoded by

DNA68862-2546 is an acyltransferase. Acyltransferases are enzymes which acylate moieties. For example, acyl-glycerol-phosphate acyltransferases can act on lysophosphatidic acid as a substrate. The lysophosphatidic acid is converted to phophatidic acid and thus plays a role in forming phosphatidylethanolamine found in membranes. See Brown, et al., Plant Mol. Biol., 26(1):211-223 (1994). Moreover, 1-acyl-sn-glycerol-3-phosphate acyltransferase (LPAAT) is an enzymatic protein that shows a preference for medium-chain-length fatty acyl-coenzyme A substrates. See, Knutson et al., Plant Physiol. 109:999-1006 (1995)). The mouse homologue of DNA68862-2546 was recently reported by Cao et al., J. Biol Chem. 279(30): 31272-31734 (2004). DNA68862-2546 and the mouse homologue (ALCAT1) discovered by Cao et al., have 73.55% homology at the nucleic acid level and 89.01% homology at the protein level. ALCAT1 was found to be an acyltransferase which serves to acylate cardiolipin, a fatty acid found in heart muscle. Thus, acyltransferases play an important role in the biosynthesis of molecules requiring acylation. Applicants have included a functional limitation in the claims that DNA68862-2546 and variants have acyltransferase activity.

In summary, therefore, the utility asserted herein is "specific" in that it describes a clear diagnostic utility and furthermore describes the specific disease conditions associated with that utility, i.e., those melanoma tumors exhibiting aberrant expression of DNA68862-2546 as compared to normal. Moreover, the utility asserted herein is "substantial" in that it provides a "currently available benefit to the public". In this regard, as described above, the legal standards for utility under 35 U.S.C. § 101 require that "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility'" (see, M.P.E.P. § 2107.01, emphasis supplied). Finally, the utility asserted herein is "credible" in that the data presented in Example 18 of the current specification clearly shows that DNA68862-2546 is detectably upregulated in at least one type of melanoma tumor when compared to the corresponding and respective normal tissue, and that satisfies the requirements of 35 U.S.C. § 101. In light of the above, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

B. The Rejection under 35 U.S.C. § 112 first paragraph

The Examiner has rejected Claims 1-20 under 35 U.S.C § 112 first paragraph as allegedly not complying with the enablement requirement. The Examiner has rejected the claims citing lack or direction for one skilled in the art to practice DNA68862-2546 polynucleotides encoding PRO3579 polypeptides that are not identical to the sequences disclosed in SEQ ID NO: 101 and SEQ ID NO: 102, as the claims lack structure or function.

Applicants have amended the claims to include that the variants in the claims comprise an acyltransferase activity. How to make DNA68862-2546 variants are disclosed in the specification and with the addition of the Applicant's limitation to the claims that the molecule have an acyltranferase activity allows one of skill in the art to make the variants and test them for acyltransferase activity to see if they fall within the scope of the claims. Therefore, one of skill in the art would be able to practice the invention. In light of the Applicant's amendments to the claims, withdrawal of this rejection is respectfully requested.

C. The Rejection under 35 U.S.C. § 112 second paragraph

The Examiner has rejected Claims 1-6, 10, and 14-20 under 35 U.S.C. § 112 second paragraph as allegedly being indefinite as to failing to point out with particularity and distinctly claim the subject matter of the invention. The Examiner objects to the recitation of the "extracellular domain" and the "extracellular domain lacking the signal sequence" as the molecule is multi-transmembrane spanner possessing several transmembrane (TM) domains. Therefore, there is no one single extracellular domain described, and there could only be one extracellular domain lacking the signal sequence. Applicants have therefore amended claims to specifically recite the amino acids given by location of the TM domain as described in Figure 102. Applicants have further deleted sections of claims with the recitation "an extracellular domain lacking the signal sequence" and canceled Claim 10. This complies with the Examiner's suggestion to clearly set forth the metes and bounds of the invention, and Applicants respectfully request withdrawal of this rejection.

The Examiner has further rejected Claim 15 under 35 U.S.C. § 112 second paragraph as allegedly being indefinite for failing to point out and distinctly claim the subject matter of the invention. The Examiner's objection to Claim 15 is that the metes and bounds of the claim is not

set forth with regards to "stringent conditions." Applicant's have therefore amended Claim 15 to specifically recite the stringent conditions for hybridization as found in the specification. Applicants therefore respectfully request withdrawal of this rejection.

D. The Rejection under 35 U.S.C. § 102(f)

The Examiner has rejected Claims 1-17 under 35 U.S.C. 102(f) as allegedly not inventing the subject matter patented. In support of this rejection the Examiner has cited Applicant's U.S. provisional application 60/170,262, that Applicants purchased a EST from Incyte Corporation and the cDNA insert was obtained and sequenced. Applicants respectfully traverse the rejection. Applicants have properly claimed priority to the provisional application 60/170,262. The Incyte EST (2377329) cited as §102(f) art and as disclosed in the database is shown graphically below in an alignment with DNA68862-2546. As one can see, the 2377329 EST sequence is only 197 bases long and aligns to the 5' end of the sequence without reaching the beginning start (ATG and STOP underlined and bolded in the alignment) of the coding region. What is not covered by the 2377329 EST is the novel sequence discovered by the Applicants.

The legal standard for derivation under 102(f) is that:

"Derivation requires complete conception by another and communication of that conception by any means to the party charged with derivation prior to any date on which it can be shown that the one charged with derivation possessed knowledge of the invention." Kilbey v. Thiele, 199 USPQ 290, 294. See also MPEP §2137

Thus the standard requires complete conception of the invention by another and communication of that conception by the opposing party. In the instant case, the Incyte 2377329 EST does not provide complete conception to one of skill in the art of the sequence of DNA68862-2546. The Applicants refer the Examiner to Example 1 of the 60/170,262 provisional, which states that Applicants performed a novel signal sequence search to identify sequences that might be of interest, the sequences were then assembled ("phrap") to determine a consensus, and then a single best choice EST clone was purchased (Incyte EST 2377329). Applicants submit that the conception of the invention began with the Applicant's bioinformatics techniques, and therefore is not derivation under §102(f). The Incyte EST 2377329 can only provide conception to what is actually disclosed, which is the 5' non-coding region of

DNA68862-2546, which leaves the rest of the DNA68862-2546 sequence undisclosed and therefore the full length DNA68862-2546 sequence could not be derived.

Furthermore, the legislative intent behind §102(f) is to prevent one from misappropriating inventions from another and obtaining patent protection. This is shown by lack of a time limit in §102(f), so that the party whose invention is misappropriated can ask the USPTO for a §102(f) rejection at <u>any</u> time and prevent the deriver from obtaining a patent, as §102(f) does not require an inquiry into the relative dates of a reference and the patent application. Applicants submit that the purchase of a partial clone from a company (Incyte) willingly selling those clones on an open market with the intent to profit from that sale is not derivation under the intent of §102(f). Therefore, as the coding region of DNA68862-2546 is not covered by the Incyte 2377329 EST, that the conception of the sequence of DNA68862-2546 was not completed by Incyte, and that the willing sale of a partial clone to a legitimate purchaser is not the purpose behind §102(f), Applicants respectfully request that this rejection be withdrawn.

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<first sequence: /home/ruby/va/Molbio/carpenda/ss.incy.2377329 (2377329), length = 197
<second sequence: /home/ruby/va/Molbio/carpenda/ss.DNA68862-2546 (DNA68862-2546),
length = 1728

<197 matches in an overlap of 197: 100.00 percent similarity
<gaps in first sequence: 0, gaps in second sequence: 0
<score: 591 (match = 3, mismatch = 0, gap penalty = 8 + 1 per base)
<endgaps not penalized

                  10         20         30         40         50
2377329H1    GGCCGGACGCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCCGCACGG
             ***************************************************
DNA68862     GGCCGGACGCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCCGCACGG
                  10         20         30         40         50

                  60         70         80         90        100
2377329H1    AGGTTGTGACCCCTACGGAGCCCCAGCTTGCCCACGCACCCCACTCGGCG
             ***************************************************
DNA68862     AGGTTGTGACCCCTACGGAGCCCCAGCTTGCCCACGCACCCCACTCGGCG
                  60         70         80         90        100

                 110        120        130        140        150
2377329H1    TCGCGCGGCGTGCCCTGCTTGTCACAGGTGGGAGGCTGGAACTATCAGGC
             ***************************************************
DNA68862     TCGCGCGGCGTGCCCTGCTTGTCACAGGTGGGAGGCTGGAACTATCAGGC
                 110        120        130        140        150

                 160        170        180        190
2377329H1    TGAAAAACAGAGTGGGTACTCTCTTCTGGGAAGCTGGCAACAAATGG
             ********************************************
DNA68862     TGAAAAACAGAGTGGGTACTCTCTTCTGGGAAGCTGGCAACAAATGGATG
                 160        170        180        190        200

DNA68862     ATGTGATATATGCATTCCAGGGGAAGGGAAATTGTGGTGCTTCTGAACCC
                 210        220        230        240        250
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DNA68862 ATGGTCAATTAACGAGGCAGTTTCTAGCTACTGCACGTACTTCATAAAGC
260 270 280 290 300

DNA68862 AGGACTCTAAAAGCTTTGGAATCATGGTGTCATGGAAAGGGATTTACTTT
310 320 330 340 350

DNA68862 ATACTGACTCTGTTTTGGGGAAGCTTTTTTGGAAGCATTTTCATGCTGAG
360 370 380 390 400

DNA68862 TCCCTTTTTACCTTTGATGTTTGTAAACCCATCTTGGTATCGCTGGATCA
410 420 430 440 450

DNA68862 ACAACCGCCTTGTGGCAACATGGCTCACCCTACCTGTGGCATTATTGGAG
460 470 480 490 500

DNA68862 ACCATGTTTGGTGTAAAAGTGATTATAACTGGGGATGCATTTGTTCCTGG
510 520 530 540 550

DNA68862 AGAAAGAAGTGTCATTATCATGAACCATCGGACAAGAATGGACTGGATGT
560 570 580 590 600

DNA68862 TCCTGTGGAATTGCCTGATGCGATATAGCTACCTCAGATTGGAGAAAATT
610 620 630 640 650

DNA68862 TGCCTCAAAGCGAGTCTCAAAGGTGTTCCTGGATTTGGTTGGGCCATGCA
660 670 680 690 700

DNA68862 GGCTGCTGCCTATATCTTCATTCATAGGAAATGGAAGGATGACAAGAGCC
710 720 730 740 750

DNA68862 ATTTCGAAGACATGATTGATTACTTTTGTGATATTCACGAACCACTTCAA
760 770 780 790 800

DNA68862 CTCCTCATATTCCCAGAAGGGACTGATCTCACAGAAAACAGCAAGTCTCG
810 820 830 840 850

DNA68862 AAGTAATGCATTTGCTGAAAAAAATGGACTTCAGAAATATGAATATGTTT
860 870 880 890 900

DNA68862 TACATCCAAGAACTACAGGCTTTACTTTTGTGGTAGACCGTCTAAGAGAA
910 920 930 940 950

DNA68862 GGTAAGAACCTTGATGCTGTCCATGATATCACTGTGGCGTATCCTCACAA
960 970 980 990 1000

DNA68862 CATTCCTCAATCAGAGAAGCACCTCCTCCAAGGAGACTTTCCCAGGGAAA
1010 1020 1030 1040 1050

DNA68862 TCCACTTTCACGTCCACCGGTATCCAATAGACACCCTCCCCACATCCAAG
1060 1070 1080 1090 1100

DNA68862 GAGGACCTTCAACTCTGGTGCCACAAACGGTGGGAAGAGAAAGAAGAGAG
1110 1120 1130 1140 1150

DNA68862 GCTGCGTTCCTTCTATCAAGGGGAGAAGAATTTTTATTTTACCGGACAGA
1160 1170 1180 1190 1200

DNA68862 GTGTCATTCCACCTTGCAAGTCTGAACTCAGGGTCCTTGTGGTCAAATTG
1210 1220 1230 1240 1250

DNA68862 CTCTCTATACTGTATTGGACCCTGTTCAGCCCTGCAATGTGCCTACTCAT
1260 1270 1280 1290 1300

DNA68862 ATATTTGTACAGTCTTGTTAAGTGGTATTTTATAATCACCATTGTAATCT
1310 1320 1330 1340 1350

DNA68862 TTGTGCTGCAAGAGAGAATATTTGGTGGACTGGAGATCATAGAACTTGCA
1360 1370 1380 1390 1400

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DNA68862    TGTTACCGACTTTTACACAAACAGCCACATTTAAATTCAAAGAAAAATGA
                  1410       1420       1430       1440       1450

DNA68862    GTAAGATTATAAGGTTTGCCATGTGAAAACCTAGAGCATATTTTGGAAAT
                  1460       1470       1480       1490       1500

DNA68862    GTTCTAAACCTTTCTAAGCTCAGATGCATTTTTGCATGACTATGTCGAAT
                  1510       1520       1530       1540       1550

DNA68862    ATTTCTTACTGCCATCATTATTTGTTAAAGATATTTTGCACTTAATTTTG
                  1560       1570       1580       1590       1600

DNA68862    TGGGAAAAATATTGCTACAATTTTTTTTAATCTCTGAATGTAATTTCGAT
                  1610       1620       1630       1640       1650

DNA68862    ACTGTGTACATAGCAGGGAGTGATCGGGGTGAAATAACTTGGGCCAGAAT
                  1660       1670       1680       1690       1700

DNA68862    ATTATTAAACAATCATCAGGCTTTTAAA
                  1710       1720
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SUMMARY

In view of the above amendments and remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

Should the Examiner not agree that all claims are allowable, then a personal or telephonic interview is respectfully invited to discuss any remaining issues and accelerate the eventual allowance of this application.

No fee is believed to be due for the submission of this response. Should any fees be required, however, please charge such fees to Genentech, Inc.'s Deposit Account No. 07-0630.

Respectfully submitted,
GENENTECH, INC.

Date: March 17, 2005

By: _____

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